## REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application are respectfully requested.

The claims have been amended relating to matters of form. In the claims, the recitations of "at least" have been deleted. Abbreviations used in the claims have been deleted in favor of defining the complete name. In addition, claims 17 and 19 have been amended to state that the monoclonal antibodies recognize an epitope of each of seven wild-type strains of the species *T. equigenitalis*. While seven strains are specified, this does not exclude monoclonal antibodies which recognize more than seven strains. The monoclonal antibodies cannot, however, recognize less than seven strains. No new matter is added by this amendment. Support for the amendment may be found at the very least at Table II, page 14 of the specification.

Claims 30, 34 and 35 are said to be directed to an independent and distinct invention from that originally claimed. The "elected invention" was said to be kits that comprise monoclonal antibodies. Claim 30 as amended is said to encompass three different kits, i.e., monoclonal antibody kits, protein kits and anti-antibody kits. The embodiments of kits with protein or anti-antibody have been deleted from the claims.

No new matter is added by these amendments. Nor are any new issues raised. Entry of these amendments is consistent with 37 C.F.R. §1.116.

Claim 17 and 31 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. This rejection is respectfully traversed.

According to the Official Action, the application does not describe a monoclonal antibody that binds to a single epitope that prevents infection and disease, or has been shown to treat pre-existing infection. The monoclonal antibodies of the invention specifically bind to the antigens of *T. equigenitalis*, but allegedly are not defined to be opsonic antibodies.

This assertion is in error. As discussed in the Declaration included herewith, the monoclonal antibodies of the instant invention have unexpectedly high sensitivity and specificity. The monoclonal antibodies of the instant invention thus are useful as diagnostic tools. In addition, due to the high sensitivity and specificity, such monoclonal antibodies could also be used to prevent or treat infection and disease.

Withdrawal of this rejection is thus believed to be in order. Such action is respectfully requested.

Claim 19 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the phrase "the required monoclonal antibodies" has been objected to. This rejection is now moot in view of the deletion of this phrase.

Claims 17, 18, 19, 22, 24, 26, 28 and 31 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Akuzawa et al. This rejection is respectfully traversed.

Claims 17, 19, 26 and 28 have been rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Friedrich. This rejection is respectfully traversed.

First, it is believed to be in error to base the rejection on only limited information from page 13 cited in the Official Action, and not include the complete teachings of the

reference. Submitted herewith is a copy of the dissertation from which page 13 is taken. A translation of the relevant pages was previously submitted. A Declaration attesting to the accuracy of the translation is also submitted herewith.

Akuzawa et al fails to disclose a monoclonal antibody as claimed in the instant application. First, Akuzawa et al does not teach a monoclonal antibody which will recognize an epitope of a bacterium of each of seven wild-type strains of the species *T. equigenitalis*. Akuzawa et al does not teach a monoclonal antibody which will recognize "an epitope of a bacterium of seven wild-type strains of the species *T. equigenitalis*." As stated in the Abstract, the monoclonal antibody of Akuzawa et al reacts with only "5 strains from 10 separate strains of wild *T. equigenitalis*." Table II of the application (Page 14) shows that the claimed monoclonal antibodies react with seven separate strains of wild *T. equigenitalis*. *See,* Gradinaru Declaration, paragraph 11.

Applicants' claims also recite that the claimed monoclonal antibodies "do not exhibit a crossed reaction with *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*." This is also shown in Table II of the application on page 14. A monoclonal antibody which does not exhibit a crossed reaction with each of these species is not shown in the reference. The reference states that the monoclonal antibody does not react with other equine uterine-infection causing bacteria, but does not disclose a monoclonal antibody that does not exhibit a crossed reaction with any of the specified bacteria. While the Abstract states that "the specificity of the monoclonal antibodies was investigated using 9 strains of bacteria other

than *T. equigenitalis* (such as *Klebsiella pneumoniae, E. coli*, and the like) derived from horse uteruses," each of the 9 strains tested are, however, not identified. Contrary to the assertion in the Official Action, that the monoclonal antibodies did not cross react with nine unidentified bacteria does not teach or suggest that the monoclonal antibodies did not cross react with the eight specified bacteria in the claims. *See,* Gradinaru Declaration, ¶12.

As further stated in the Gradinaru Declaration:

> 13. The monoclonal antibodies of Akuzawa et al cannot be used in a diagnostic kit as instantly claimed. As stated in the "Results" section, the monoclonal antibodies reacted with only 5 out of 10 strains of wild *T. equigenitalis*. Since Akuzawa et al's monoclonal antibodies react with only some strains of *T. equigenitalis*, they could not be used in a diagnostic kit, as instantly claimed. By comparison, applicants' monoclonal antibodies reacted with all seven separate strains of wild *T. equigenitalis* against which they were tested.

Akuzawa et al thus fails to disclose or even suggest the claimed invention. Withdrawal of the rejection of record is respectfully requested and believed to be in order.

Claim 18 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Friedrich in view of Sugimoto. This rejection is respectfully traversed.

This rejection is somewhat unclear. In the comments on page 10, the rejection appears to be based on the combination of Friedrich with Akuzawa et al rather than with Sugimoto et al, as set forth in the actual rejection. Clarification is requested.

Friedrich fails to disclose or even suggest the claimed invention. On page 7 of the Official Action, last paragraph, it states that page 19 of the translation states: "In the study of potential cross-reactions of all the mAb used with representatives of different bacterial species, no antigenic affinities could be detected." The translation is also cited for the statement "[S]ince the mAb TF II8D4 and TF III 11B5 detect all the Taylorella strains under test with the ELISA technique, did not show any cross-reactions with previously tested bacterial species and these antibodies are able to react with the IFT technique, it is possible to establish a rapid test based on IFT." The sentence which follows that quoted from page 19 states: "Potential antigenic affinity of T. equigenitalis with streptococcus zooepidemicus and Streptococcus equi cannot be proven due to the non-specific fixation of the conjugate used represented in the figure (Fig. 19)."

The claims require that the monoclonal antibodies of the claims "not exhibit a crossed reaction with *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*." Since Friedrich's monoclonal antibodies may have a crossed reaction with at the very least *Streptococcus equi*, it fails to disclose or suggest applicants' invention. The translation of the dissertation does not show a monoclonal antibody which does "not exhibit a crossed reaction with *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*." *See,* Gradinaru Declaration, ¶17.

Friedrich does not teach a monoclonal antibody that does not exhibit a crossed reaction with any of the claimed species, much less one that does not exhibit a crossed reaction with each of them. In particular, *Steptococcus equi* is a very common bacteria in females. A monoclonal antibody which can distinguish between *T. equigenitalis* and *Steptococcus equi* would thus be very advantageous over the prior art, and would eliminate many false positives. Since the monoclonal antibody of Friedrich is disclosed as possibly exhibiting a crossed reaction with *Streptococcus equi*, Friedrich does not teach a monoclonal antibody that can make the distinction between *T. equigenitalis* and *Steptococcus equi*. Friedrich thus does not disclose a monoclonal antibody that can used in a kit to detect a bacterium of the species *T. equigenitalis* in a specimen or in a culture. By contrast with Friedrich, the instantly claimed monoclonal antibodies will avoid false positives from other species, such as *Streptococcus equi*. *See,* Gradinaru Declaration, ¶18.

In the instant invention, the monoclonal antibodies were prepared and tested. They were tested using the various strains of *T. equigenitalis* and the strains of other bacteria commonly found in females. As shown in Table II, the monoclonal antibodies of the invention do not cross react with the various other bacteria strains tested and do cross react with all of the bacteria cited, which are common in females.

Additional results relating to the invention are also discussed in the Gradinaru Declaration:

20. Results relating to this invention were presented in an abstract and poster at the IXth International Symposium of Veterinary Laboratory Diagnosticians,

on June 2-5, 1997, at College Station, Texas, USA. The Abstract is attached hereto as Appendix B. As shown therein, the monoclonal antibodies of the invention were used in an indirect immunofluorescence (IIF) test to evaluate their sensitivity and specificity. Several experiments were done.

21. In the first experiment, the claimed monoclonal antibodies detected 4 reference strains and 253 (97,7%) out of 259 field strains, as tested by French Reference Laboratory of Contagious Equine Metritis (CEM).

22. In the second experiment, five French State Veterinary Laboratories compared the results of 1014 routinely CEM swabs by three methods: IIF using the monoclonal antibodies of the invention, IIF using polyclonal antibodies, and culture. In this test, the culture was considered the reference test. Out of 1014 samples, only one *Taylorella equigenitalis* was isolated and identified in culture, but 58 (6%) were positive with the IIF-Mabs kit and 409 (40%) with the polyclonal IIF test.

23. This experiment shows a sensitivity of 97.7% and specificity of 94%, the indirect immunofluorescence test using monoclonal antibodiescould be a valuable test for the diagnosis of contagious equine metritis.

As concluded by Dr. Gradinaru: "These experiments show the beneficial and unexpected results achieved by the instant invention. It would not have been known, prior to the instant invention, that such sensitivity and specificity could be achieved." *See,* Gradinaru Declaration, ¶24.

Friedrich's monoclonal antibodies thus have not been shown to possess the characteristics of the monoclonal antibodies now claimed. Friedrich's monoclonal antibodies do not have the sensitivity or specificity of the instantly claimed invention. They would, therefore, not be useful in a diagnostic kit as instantly claimed. Friedrich has 2 mAbs, TFII8D4 and TFIII11B5, as shown on page 18. As shown in Table II of the specification, applicants' monoclonal antibodies have a specific pattern for cross reacting with other species and not being cross-reactive with others. Table III of Friedrich shows that the monoclonal antibodies of the claims detect activity. However, no activity was shown for Friedrich from the results using the immunoblot technique. An immunoblot is used in the art to show specificity of an antibody. When testing an antibody for activity, if there is no reaction, then specificity is not known for the antibody.

For the reasons set forth *supra*, Friedrich does not disclose or suggest a monoclonal antibody as claimed in the instant application. Nor does Sugimoto overcome or remedy the deficiencies of Friedrich.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claim 18 has been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Friedrich in view of Corbel et al. This rejection is respectfully traversed.

According to the Examiner, Friedrich taught the production of monoclonal antibodies to *T. equigenitalis* antigens to have the advantage of a better proof and prompt diagnosis of infection. Corbel et al is cited as characterizing major *T. equigenitalis*

antigens to include polysaccharide surface antigens, shown to be immunogenic and immunoreactive. Eleven antigens were disclosed and the molecular weights provided. The Examiner asserts that one skilled in the art would be motivated to produce monoclonal antibodies to the major antigens of *T. equigenitalis* for prompt diagnosis of infection in horses associated with reproductive failure.

For the reasons set forth *supra*, Friedrich fails to disclose or even suggest the production of monoclonal antibodies as instantly claimed, which would provide better proof and prompt diagnosis of infection. As discussed *supra*, Friedrich does not provide the high sensitivity and specificity of the instant invention.

The teachings of Corbel fail to overcome or remedy these deficiencies.

Withdrawal of the rejection is thus respectfully requested and believed to be in order.

Claims 17, 19, 22, 24, 26, 28-29, 31, 35 and 37 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Tainturier et al in view of Friedrich and Harlow. This rejection is respectfully traversed.

The Examiner asserts that Friedrich and Harlow provide motivation and reasonable expectation of success for obtaining non-cross reactive monoclonal antibodies that provide an advantage over monoclonal antibodies. Tainturier et al is said to teach the importance of non-cross reactive antibodies and specific antigens found only in *T. equigenitalis*. The combination of references is said to provide motivation and reasonable expectation of success for obtaining monoclonal antibodies specific to *T. equigenitalis* antigens, the antibodies being diagnostic reagents for diagnosis of infection.

As set forth above, Friedrich fails to teach non-cross reactive monoclonal antibodies that are advantageous. Nor does Harlow disclose such antibodies as instantly claimed, having such high specificity or sensitivity, as discussed in the Gradinaru Declaration. The teachings of the combination of reference thus fails to disclose or even suggest monoclonal antibodies diagnostic of infection as claimed herein.

Withdrawal of the rejection is thus respectfully requested and believed to be in order.

Claims 30, 33 and 34 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Tainturier in view of Friedrich and Harlow further in view of Foster. This rejection is respectfully traversed.

Foster is cited as teaching the formulation of kits and components for an immunoassay. The deficiencies of Tainturier, Friedrich and Harlow are discussed *supra*. The cited teaching of Foster fails to overcome or remedy those deficiencies.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

Claims 17-19, 22, 24, 26, 29, 35, 28, 27, 20, 33, 34 and 31 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification. This rejection is rendered moot by the instant amendment.

The recitation of "at least" has been deleted from the claims. However, as stated *supra*, the list of bacteria is not exhaustive of the bacteria with which the monoclonal antibodies are not cross-reactive. The monoclonal antibodies must not be cross-reactive

with the specified species. However, the monoclonal antibodies may also not be cross-reactive with additional species.

Withdrawal of the rejection of record is thus respectfully requested and believed to be in order.

In view of the above, it is respectfully submitted that none of the cited references either alone or in combination disclose or suggest applicants' claimed invention. Withdrawal of the rejections of record, as they apply to the claims now of record, are respectfully requested and believed to be in order.

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (650) 622-2360 so that prosecution of the application may be expedited.

Respectfully submitted,

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**Attachment to Reply and Amendment dated April 11, 2003**

**Marked-up Claims 17, 19, 23, 26-28, 30 and 38**

17. (Thrice Amended) Isolated monoclonal antibodies or their Fv, Fab, and $F(ab')^2$ fragments, which recognize an epitope of a bacterium of each of seven wild-type strains of the species *Taylorella equigenitalis* (*T.* equigenitalis), and which do not exhibit a crossed reaction with [at least *K pneumoniae, Psfluorescens, St aureus, Str aqui, P haemolytica, P multocida, Ps aeruginosa and Act equuli*] *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*.

19. (Thrice Amended) Isolated monoclonal antibodies, which can be obtained from hybridomas by a method comprising:

fusing non-secreting murine myeloma cells with spleen cells from mice immunized against an inactivated strain of the species *Taylorella equigenitalis* (*T.* equigenitalis) or extract(s) of such a strain,

cloning and selecting according to the capacity of their culture supernatant to recognize an epitope or epitopes of a bacterium of each of seven wild-type strains of the species *T. equigenitalis*, and to not exhibit a crossed reaction with [at least *K pneumoniae, Psfluorescens, St aureus, Str aqui, P haemolytica, P multocida, Ps aeruginosa and Act equuli*] *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*,

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**Marked-up Claims 17, 19, 23, 26-28, 30 and 38**

recovering the [required] monoclonal antibodies, and

optionally purifying said monoclonal antibodies.

23. (Twice Amended) A method of obtaining monoclonal antibodies according to claim 21, comprising:

fusing non-secreting murine myeloma cells with spleen cells from mice immunized by means of monoclonal antibodies or their Fv, Fab, and F(ab')2 fragments, which recognize an epitope of a bacterium of the species *T. equigenitalis*, and which do not exhibit a crossed reaction with at least [*K pneumoniae, Psfluorescens, St aureus, Str aqui, P haemolytica, P multocida, Ps aeruginosa and Act equuli*] *Klebsiella pneumoniae, Pseudomonas fluorescens, Staphylococcus aureus, Streptococcus equi, Pasteurella haemolytica, Pasteurella multocida, Pseudomonas aeruginosa* and *Actinobacillus equuli*,

screening hybridomas whose culture supernatants exhibit a positive reaction with one of the said monoclonal antibodies or their fragments,

selecting by cloning the hybridomas, and

recovering the required anti-antibodies.

26. (Twice Amended) A method of identification of a bacterium of the species *Taylorella equigenitalis* (*T.* equigenitalis) in a specimen or in a culture comprising:

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**Marked-up Claims 17, 19, 23, 26-28, 30 and 38**

bringing the specimen or the culture to be analyzed, which may contain *T. equigenitalis*, into contact with an effective quantity of at least one monoclonal antibody or Fv, Fab, or F(ab')2 fragment thereof according to claim 17, under conditions permitting a reaction of the antigen-antibody type, and

detecting any product formed in a reaction of the antigen-antibody type.

27. (Amended) A method of identification of a bacterium of the species *Taylorella equigenitalis* (*T.* equigenitalis) in a specimen or in a culture comprising:

bringing the specimen or the culture to be analyzed which may contain *T. equigenitalis* into contact, under conditions permitting a reaction of the antigen-antibody type, with an effective quantity of a compound selected from the group consisting of an immunogenic protein and a monoclonal anti-antibody or Fv, Fab, and F(ab')2 fragment thereof, wherein said protein and anti-antibody or fragment thereof are capable of interacting with monoclonal antibodies or their fragments according to claim 17, so as to detect the presence of antibodies directed against *T. equigenitalis*, and

detecting any product formed in a reaction of the antigene antibody type.

28. (Amended) Method of diagnosis of an infection by *Taylorella equigenitalis* (*T.* equigenitalis) comprising:

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**Marked-up Claims 17, 19, 23, 26-28, 30 and 38**

bringing one or more monoclonal antibodies according to claim 17 or their fragments, into contact with a biological sample, and

detecting the reaction of the antigen-antibody type which is produced when *T. equigenitalis* is present in the sample.

30. (Thrice Amended) Kits for application of a method of identification of a bacterium of the species *Taylorella equigenitalis* (*T.* equigenitalis) in a specimen or in a culture, which include:

[at least one compound selected from the group consisting of] a monoclonal antibody or fragment according to claim 17, [an immunogenic protein and a monoclonal anti-antibody or fragment thereof are capable of interacting with said monoclonal antibody or fragment thereof,]

reagents, for detecting the intended immunologic reaction,

optionally, reagents for blocking the non antigen-antibody reactions, and

instructions for use.

38. (Amended) A method of obtaining a protein selected from the group consisting of *Taylorella equigenitalis* (*T.* equigenitalis) immunogenic proteins and *T. equigenitalis* anti-antibodies, comprising the use of a monoclonal antibody or fragment according to claim 17.